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Irritable bowel syndrome patients show altered sensitivity to exogenous opioids

Tony Lembo[a], Bruce D. Naliboff[b,c], Kamran Matin[c], Julie Munakata[c], Robert A. Parker[a], Richard H. Gracely[d], Emeran A. Mayer[c,e,*]

[a]*Department of Medicine, Beth Israel Deaconess Hospital, Boston, MA, USA*
[b]*Department of Psychology and Biobehavioral Sciences, UCLA/West Los Angeles VA Healthcare Center, Los Angeles, CA, USA*
[c]*CURE Digestive Diseases Research Center/Neuroenteric Disease Program, Department of Medicine, UCLA School of Medicine, Los Angeles, CA, USA*
[d]*CMMU, PNMB, NIDCR, NIH, Bethesda, MD, USA*
[e]*Department of Physiology, UCLA School of Medicine, Los Angeles, CA, USA*

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Abstract

Alterations in activation of pain modulation systems may play a role in the pathophysiology of irritable bowel syndrome (IBS). However, little is known about the effects of exogenous opioids on the perceptual and autonomic responses to aversive visceral stimulation. The aim of the study was to evaluate the effect of the mu opioid-preferring analgesic fentanyl (FEN), given intravenously, on perceptual and autonomic responses to rectal distension. Ten IBS patients and ten normal subjects received, on separate days, either high dose (HD) fentanyl (112 μg bolus followed by 0.04 μg/kg per min infusion), low dose (LD) fentanyl (56 μg bolus followed by 0.02 μg/kg per min) or normal saline (SAL) (50 cc bolus followed by 45 cc/h infusion). Perception thresholds for discomfort and pain during rectal distension were assessed using a tracking paradigm. Intensity and unpleasantness ratings of the distensions, and cardiac autonomic parameters were assessed during randomly delivered rectal stimuli. Effects of FEN on rectal compliance and tone as well as mental status were also assessed. IBS patients had lower perceptual thresholds for discomfort and pain under control conditions. FEN dose-dependently increased the perception thresholds in both healthy control subjects and in IBS patients with a greater relative efficacy in IBS patients than in normal subjects. IBS patients used significantly higher unpleasantness ratings of rectal stimuli compared to healthy controls, but showed no difference in the sensory intensity rating of the stimulus. FEN decreased both intensity and unpleasantness ratings for IBS and normals. FEN lowered cardiosympathetic tone in normal subjects but had no effect on IBS patients. FEN had no effect on rectal tone or compliance. FEN dose-dependently attenuates the perception of phasic rectal distension and affects unpleasantness ratings during random fixed rectal distension, with a greater relative efficacy for this antinociceptive effect in IBS patients. These findings support the hypothesis that IBS patients may have an altered central release of endogenous opioids in response to visceral stimulation.

Keywords: Fentanyl; Antinociception; Visceral pain

1. Introduction

Patients suffering from IBS show several clinical and experimental findings suggesting an enhanced sensitivity to certain types of visceral stimulation (Mayer and Gebhart, 1994; Naliboff et al., 1997, 1998). The most common perceptual abnormality is an increased vigilance towards expected aversive events, which manifests as early labeling of predictable visceral stimuli as aversive, and as a decreased tolerance for such stimuli. A second abnormality is the development of rectosigmoid hyperalgesia following a train of repetitive noxious sigmoid distensions in the majority of IBS patients, but not in healthy controls (Munakata et al., 1997) or in patients with mild inflammatory bowel disease (Chang et al., 2000). In the absence of detectable tissue damage or irritation, alterations in the activation of endogenous pain modulation systems, either in response to physiological visceral events, or in response to anticipated aversive visceral events, can be considered as a plausible pathophysiological mechanism (Fields et al., 1991; Mayer and Gebhart, 1994; Wei et al., 1999).

Alterations in activation of pain modulation systems have

* Corresponding author. UCLA Division of Digestive Diseases, WLA VA Medical Center, Building 115/CURE, 11301 Wilshire Boulevard, Los Angeles, CA 90073, USA. Tel.: +1-310-312-9276; fax: +1-310-794-2864.
E-mail address: emayer@ucla.edu (E.A. Mayer).

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been postulated to play a role in a variety of chronic syndromes characterized by discomfort and pain, but without detectable structural abnormalities. Such chronic pain and discomfort could result from enhanced activation of pain facilitatory systems and/or from inadequate activation of pain inhibitory systems (Wei et al., 1999). The brainstem region that plays a role in the activation of these systems are neurons within the rostral ventral medulla (RVM) which are modulated by endogenously released opioids. Endogenously released or exogenously applied opioids reduce pain by inhibiting 'on cells' and disinhibiting 'off cells' in the RVM (Fields et al., 1991). 'On cells' give rise to pain facilitatory systems and their output inhibits pain inhibitory systems. Inbred mouse strains that show evidence for a failure to activate pain inhibitory systems have been found to show diminished mu opioid receptor density in the periaqueductal grey (PAG) and this diminished receptor number is associated with a decreased sensitivity to morphine (Mogil et al., 1996a). Similarly, mu opioid receptor knock-out mice do not show an analgesic response to exogenously administered mu opioid agonists (Matthes et al., 1996).

Neurons within the RVM receive input from several forebrain and midbrain regions involved in pain modulation, such as the anterior cingulate cortex, PAG, hypothalamus and the medial thalamus (Holstege, 1987). Recent evidence from brain imaging studies using PET suggests that compared to healthy control subjects, IBS patients show less activation of a brain region reaching from the thalamus to the PAG in response to repetitive noxious sigmoid distension (Mayer et al., 1998). Since repetitive sigmoid distension induces rectosigmoid hyperalgesia in IBS patients, but not healthy control subjects, we hypothesized that in IBS patients, enhanced sensitivity to rectal distension may be at least partially related to altered descending pain modulation of visceral afferent input. In analogy to inbred mouse strains in which decreased stress-induced analgesia is associated with decreased morphine antinociception (Mogil et al., 1996b), such failure could result either from a diminished number of mu opioid receptors (MOR) within the brain, or from a failure to release sufficient quantities of endogenous opioids in response to noxious stimuli. A diminished number of central MORs should result in a diminished response to exogenously administered opioids, whereas a diminished release should produce a greater response. The analgesic effect of exogenous opioids is mediated by a widely distributed network ranging from opioid receptors on peripheral terminals of primary afferents to opioid receptors in the frontal cortex (Fields et al., 1991; Manning, 2000). Even though each site is capable of contributing to the overall analgesic effect, opioid actions within regions of the limbic system may be essential for the analgesic and antinociceptive effects of morphine or fentanyl.

In the current study, we wanted to explore this hypothesis by evaluating the effect of the MOR-preferring analgesic fentanyl (FEN), given intravenously, on perceptual responses to rectal distension and on simultaneously recorded cardioautonomic responses. Specifically, we wanted to address the following questions. (1) Does FEN increase discomfort thresholds and attenuate intensity ratings during phasic rectal distension? (2) Does FEN attenuate cardiosympathetic responses associated with distension? (3) Do IBS patients show a diminished sensitivity to FEN, compared to healthy control subjects, suggesting a decreased number of central MORs? (4) Do IBS patients show an enhanced response to FEN, compared to healthy controls, suggesting a diminished release of endogenous opioids in response to visceral stimulation?

2. Methods

2.1. Subjects

2.1.1. Normals

Eleven healthy control subjects (six women and five men; mean age 39.4 years, range 21–58 years) without evidence of an acute or chronic illness were recruited by newspaper advertisement. In particular, there was no evidence in any of the subjects of an acute or chronic pain syndrome, drug abuse, or abdominal symptoms either by bowel symptom questionnaire, personal history, or physical examination. Healthy control subjects were chosen so that they were a similar age and gender to that of the IBS patients.

2.1.2. IBS patients

Eleven patients with IBS (six women and five men; mean age 40.6 years, range 25–63 years) were recruited from the UCLA Center for Functional Bowel Disorders and by newspaper advertisement. Selection criteria included a positive diagnosis by the 'Rome' criteria (Thompson et al., 1992), the presence of three or more Manning criteria (Manning et al., 1978), a clinical diagnosis of IBS made by gastroenterologists experienced in the diagnosis of functional bowel disorders (T.L., E.A.M.), and the exclusion of organic disease. Patients on or reporting a history of narcotic or pain medication use, or current use of medications known to affect the gastrointestinal tract were excluded from participation in the study.

Verbal and written informed consent was obtained from each subject. This study was approved by the West Los Angeles VA Medical Center Research and Development Committee and Committee on Human Studies.

2.2. Materials – visceral stimulation device

Distension of the rectum was performed by air inflation of a single latex balloon (9 cm in length) attached to a Silastic elastomer tube (external diameter 18 F) and tied at both proximal and distal ends (MAK-LA, Los Angeles, CA). The use of a computer-driven volume displacement device allowed for controlled inflation of the balloons. The distension device was programmed to simultaneously record pres-

sures and volumes (sampling rate 1/s), and to log the sensations (i.e. no sensation, moderate sensation, discomfort, and pain) from a push-button marker device onto a data file. We have previously validated the response characteristics of the distension device (Lembo et al., 1994).

2.3. Experimental protocol

All studies were performed after an 8 h fast and application of two Fleet enemas (C.B. Fleet Co Inc., Lynchburg, VA). All medications known to affect the gastrointestinal tract were discontinued 48 h before the procedure. The lubricated balloon was placed into the rectum such that the distal end of the balloon was 4 cm from the anal orifice and the catheter was secured with tape. All balloon stimulation studies were performed 30 min after balloon placement. Subjects were placed in the left lateral decubitus position on a padded table. Although the examiner was always present, interaction with the subjects ceased after initial explanation of the respective task. Subjects had no visual or auditory cues to anticipate the location or time course of distensions, and they were not instructed about the nature of the distension protocols. Two distension protocols, sensory tracking and fixed-stimulus (see below), were used to evaluate rectal perception. Protocols were administered in a random order.

All subjects underwent testing on 3 separate days 1 week apart at the same time of day. Sessions were identical except for the content of the intravenous infusion which was either FEN (112 μg bolus followed by 0.04 μg/kg per min infusion) (high dose, HD), FEN (56 μg bolus followed by 0.02 μg/kg per min) (low dose, LD), or normal saline (50 cc bolus followed by 45 cc/h) (normal saline, SAL). Subjects and the technician operating the study (K.M.) were blinded to the contents of the infusion. For safety reasons the physician who administered the intravenous infusion had knowledge of the contents of the intravenous fluid but was present only as an observer throughout the entire study (T.L.). The order of infusions was administered randomly. All patients were monitored throughout the study with continuous pulse oximetry and by automatic blood pressure recordings at 10-min intervals. Rectal sensory testing began 20 min after the completion of the bolus infusion.

One IBS patient and one normal subject dropped from the study secondary to side effects from the FEN. The IBS patient experienced fatigue and headache during infusion of the HD bolus. This subject had tolerated LD without difficulty. The normal subject refused, for personal reasons, to return after completing the HD and SAL. Analysis of data was therefore based on ten subjects in each group.

2.3.1. Threshold tracking paradigm

Details of the threshold tracking have previously been reported (Munakata et al., 1997). Briefly, the electronic distension device was programmed to deliver intermittent phasic stimuli (15 s duration; 5 mmHg increments) separated by an interpulse interval (30 s duration; 5 mmHg) within a stimulus tracking paradigm (600 s duration; 14 distension trials). All IBS patients and controls completed the entire number of distension trials. During each stimulus and rest, subjects were prompted by the distension device to report the intensity of their sensations by triggering the push-button marker device. If the sensation indicated by the patient was below the discomfort level (i.e. no sensation or moderate) the next stimulus was increased by 5 mmHg. If the sensation indicated by the patient was discomfort, the next stimulus was randomized to stay the same or to decrease by 5 mmHg. If the sensation indicated by the patients was painful, the next stimulus was always decreased by 5 mmHg. Immediately following the tracking protocol subjects were asked to rate the symptoms experienced during the preceding tracking protocol using descriptor anchored analog scales for the unpleasantness and intensity of the stimulus.

2.3.2. Fixed stimulus paradigm

A random series of 15 rectal balloon distensions (30 s duration followed by 30 s at 5 mmHg) at constant pressures was delivered. Pressures used ranged from 20 to 60 mmHg at 10 mmHg intervals. For analysis, only pressures from 20 to 50 mmHg were used because the balloon pressure failed to reach 60 mmHg during the 30-s inflation period in six IBS and five normal subjects. Each pressure was delivered three times. Immediately following each distension, subjects were asked to (1) rate the intensity and unpleasantness of the sensation using descriptor anchored analog scales, and (2) choose from a list of sensory descriptors the sensation(s) which most precisely characterized their sensations.

2.3.3. Impairment of mental status

At the completion of each study, subjects were asked to rate on a scale from 0 to 10 the effect of the substance they received that day as to its effect on their (1) overall performance, (2) mental status, (3) judgment, and (4) clumsiness. Subjects were also asked whether they believed they received the placebo or active substance, and whether they received HD or LD FEN.

2.3.4. Cardioautonomic parameters

Electrocardiographic measurements for heart rate and beat-to-beat variability were recorded continuously (sampling rate, 1 kHz) (BIOPAK Systems, Inc., Santa Barbara, CA). Prior to electrode placement, the skin surface was cleaned with an isopropyl alcohol preparatory pad. To measure skin conductance, electrodes (8 mm diameter, silver-silver chloride) were filled with electrode gel (TECA, Pleasantville, NY) and attached by adhesive collars to the middle phalanges of the second and third fingers on the non-dominant hand. To measure heart rate and beat-to-beat variability, disposable EKG monitoring electrodes (3M Healthcare, St. Paul, MN) were attached to the chest.

2.4. Evaluation of outcome parameters

2.4.1. Thresholds

Perception thresholds for rectal discomfort were determined from the tracking protocol and expressed in reference to intrarectal pressure, volume, and wall tension as previously described (Mertz et al., 1995). Discomfort thresholds were computed by averaging the last six pressures of the rectal sensory tracking protocol. We have previously shown that the length of the task (600 s) is sufficient to give stable discomfort thresholds (Naliboff et al., 1997). Pain thresholds were determined by averaging the pressure stimuli for which the subject reported pain. In the event that pain was not reported, the pain threshold was estimated conservatively by adding 5 mmHg to the patient's discomfort threshold.

2.4.2. Stimulus ratings

The subjective intensity and unpleasantness of the rectal stimulus-evoked sensations were assessed by validated descriptor anchored analog scales (Gracely et al., 1978). The sensory scale consisted of descriptors of increasing intensity ranging from 'no sensation' to 'extremely intense', while the unpleasantness scale used descriptors ranging from 'neutral' to 'very intolerable'. In both cases the scales were arrayed along a 20 cm vertical bar and the results assigned a numerical value. Ratings were assessed immediately after each task.

2.4.3. Stimulus-response (S-R) curves

S-R curves were generated by plotting the mean intensity and unpleasantness ratings during each pressure distension during the rectal fixed stimuli protocol.

2.4.4. Stimulus discrimination

An omega^2 statistic was computed for each subject's sensory ratings from the random fixed stimulus protocol as a measure of discrimination or reliability of ratings. Essentially, this statistic compares the variance of the three ratings within a pressure step to that across pressure steps and can be interpreted as the ability to discriminate changes in pressure.

2.4.5. Verbal descriptors

Following each fixed stimulus distension at 40 mmHg, subjects were asked to indicate whether or not any of the following symptoms were present: no sensation, rectal pressure, urgency, stool, abdominal discomfort, fullness, pain, or gas.

2.4.6. Cardioautonomic parameters

Overall changes in cardiovascular regulation were assessed by averaging the heart rate obtained during the rectal sensory tracking protocol. In addition, the cardiopulmonary vagal tone was determined from the magnitude of cardiac-respiratory coupling (respiratory sinus arrhythmia) using spectral analysis of EKG beat-to-beat variability (Kamath and Fallen, 1993). The EKG signal was visually inspected for artifact and converted to interbeat intervals using a peak detection algorithm. The interbeat intervals were then resampled using linear interpolation to obtain an equally spaced series of 0.5 s samples from which the power spectrum was computed. Separate peak power measurements were determined for the low frequency (parasympathetic and sympathetic influences) and high frequency (parasympathetic or vagal influence) components of heart rate.

2.4.7. Resting volume (tone)

Volumes required to maintain a pressure of 5 mmHg during the rest interval (30 s) of the rectal sensory tracking protocol were recorded. Changes in resting volume were used as an estimate of rectal tone in response to repeated distension.

2.4.8. Rectal compliance

The compliance of the rectum was calculated by dividing the mean maximal volume (ml) required to maintain 40 mmHg during the fixed stimuli protocol.

2.4.9. Wall tension

Wall tension was estimated to express perceptual thresholds in reference to wall tension in addition to pressure. Although the precise geometry of the rectum is unknown, wall tension was estimated by assuming a cylinder of length 9 cm (balloon length) (Mertz et al., 1995). The radius at each pressure stimulus was derived from the volume of the cylinder ($V = \pi r^2 L$, where $L = 9$ cm). Wall tension was calculated from the estimated balloon radius and the derived pressure using Laplace's law (cylinder, $T = 2pr$, where p is pressure).

2.4.10. Mental status

The subject's self-assessed evaluation of functional impairment was assessed using a scale from 0 (no effect) to 10 (maximal effect) for overall performance, mental status, judgment and clumsiness.

2.5. Statistical analysis

Analysis of S-R curves was preformed using a mixed model analysis of variance, which allows for incomplete data and various correlation structures for repeated measurements. Measurements were treated as repeated within a subject and the three replications of each level of the fixed stimuli were averaged. Model strategies used tested the following: (1) whether there was a pressure effect for each group and condition; (2) whether there was a dose effect after adjusting for pressure within a group for the two FEN doses; (3) if no dose effect was found then the analysis tested whether there was a FEN effect within a group, after adjusting for pressure; and then (4) whether there was a

group effect after adjustment for other factors (e.g. pressure, FEN). Interactions were routinely tested as well.

3. Results

3.1. Clinical characteristics

Table 1 summarizes the clinical characteristics of the ten patients with IBS. No significant group difference in age or sex was observed between IBS patients and controls.

3.2. Perception thresholds and intensity ratings obtained during the threshold tracking paradigm

3.2.1. Thresholds

3.2.1.1. Normals. FEN increased mean discomfort thresholds expressed as balloon pressure during the threshold tracking paradigm (SAL 40 ± 4 mmHg; LD 46 ± 4 mmHg; HD 58 ± 4 mmHg; $P = 0.009$) (Fig. 1). HD produced a 47 ± 7% increase in discomfort threshold compared to SAL. FEN also increased the threshold at which subjects reported the first onset of pain (SAL 49 ± 3 mmHg; LD 56 ± 3 mmHg; HD 64 ± 3 mmHg; $P = 0.01$). HD produced a 28 ± 5% increase in pain threshold compared to SAL. FEN produced no significant increase in the mean volume (ml) of distension for discomfort thresholds (SAL 250 ± 31; LD 330 ± 41; HD 313 ± 42; $P = 0.15$). When perception thresholds for discomfort where expressed in terms of wall tension, no statistically significant effect of FEN was observed (SAL 63.8 ± 6.5; LD 71.1 ± 7.8; HD 83.2 ± 9.6; $P = 0.10$).

3.2.1.2. IBS. Mean discomfort thresholds in IBS patients were also significantly increased by FEN (SAL 33 ± 3 mmHg; LD 43 ± 5 mmHg; HD 54 ± 5 mmHg; $P = 0.016$) (Fig. 1). HD produced a 61 ± 9% increase in discomfort threshold compared to SAL. FEN also increased the threshold at which subjects reported the first onset of pain (SAL 40 ± 4 mmHg; LD 48 ± 4 mmHg; HD 65 ± 7 mmHg; $P = 0.01$ for HD versus SAL). HD produced a 62 ± 10% increase in pain threshold compared to SAL. HD increased discomfort thresholds when expressed in terms of distension volume (SAL 158 ± 18; LD 194 ± 27; HD 258 ± 35; $P = 0.05$). Mean wall tension for discomfort thresholds significantly increased with FEN (SAL 46 ± 5.5; LD 60.6 ± 8.0; HD 94 ± 14.4; $P = 0.03$).

Table 1
IBS patient characteristics

Age (years)	40.6 ± 10
Sex (F/M)	6:4
Average number of Manning criteria	3.6
Bowel pattern	
Constipation-predominant	36%
Diarrhea-predominant	27%
Alternating	37%
Self-rated symptom severity	
Moderate	54%
Severe	27%
Very severe	19%
Descriptor anchored scale ratings of symptoms (0–20)	
Intensity (sensory)	11 ± 1 cm (moderate)
Unpleasantness (affective)	8 ± 1 cm (very unpleasant)

3.2.1.3. IBS versus normals. During SAL infusion, mean discomfort thresholds were lower in IBS patients (SAL 33 ± 2 mmHg) in comparison to normals (SAL 40 ± 3 mmHg) ($P < 0.05$). FEN infusion normalized discomfort thresholds. During LD and HD infusion, mean discomfort thresholds were similar between IBS patients (LD 43 ± 5 mmHg; HD 54 ± 5 mmHg) and normals (LD 46 ± 4 mmHg; HD 58 ± 4 mmHg) ($P = 0.7$ for LD; $P = 0.6$ for HD). HD, in comparison to SAL, produced a significantly greater increase in discomfort thresholds for IBS patients (61 ± 9%) in comparison to normals (47 ± 7%) ($P < 0.05$). Similarly, during SAL, mean thresholds for the first report of pain were lower in IBS patients (40 ± 4 mmHg) in comparison to normals (49 ± 3 mmHg) ($P < 0.05$); however, during LD and HD infusion mean thresholds for the first use of pain were similar between IBS (LD 48 ± 4 mmHg; HD 65 ± 7 mmHg) and normals (LD 56 ± 3 mmHg; HD 64 ± 3 mmHg) ($P = 0.3$ for LD; $P = 0.7$ for HD). HD, in comparison to SAL, produced a two-fold greater increase in mean thresholds for the first use of pain in IBS patients (62 ± 10%) in comparison to normals (28 ± 5%) ($P < 0.005$). IBS patients had lower discomfort thresholds in terms of wall tension in comparison to normals during SAL infusion ($P < 0.05$), while during FEN infusion mean wall tension between IBS patients and normals was not statistically different ($P = 0.09$ for LD; $P = 0.63$ for HD).

3.2.2. Stimulus ratings

3.2.2.1. IBS. FEN significantly decreased the sensory intensity (SAL 9.1 ± 1.5; LD 6.5 ± 1.2; HD 4.0 ± 0.6; $P < 0.05$) and unpleasantness (SAL 11.1 ± 1.2; LD 9.3 ± 1.0; HD 6.6 ± 0.5; $P < 0.05$) ratings for the threshold tracking procedure in IBS patients (Fig. 2).

3.2.2.2. Normals. FEN also significantly decreased the unpleasantness rating (SAL 9.2 ± 1.1; LD 7.5 ± 1.2; HD 6.0 ± 0.6; $P < 0.05$) for the rectal tracking procedure for normals, but not the sensory intensity ratings (data not shown).

3.2.2.3. IBS versus normals. No significant differences were present between IBS patients and normals in sensory or unpleasantness ratings for the rectal tracking procedure during SAL or FEN infusion (LD or HD).

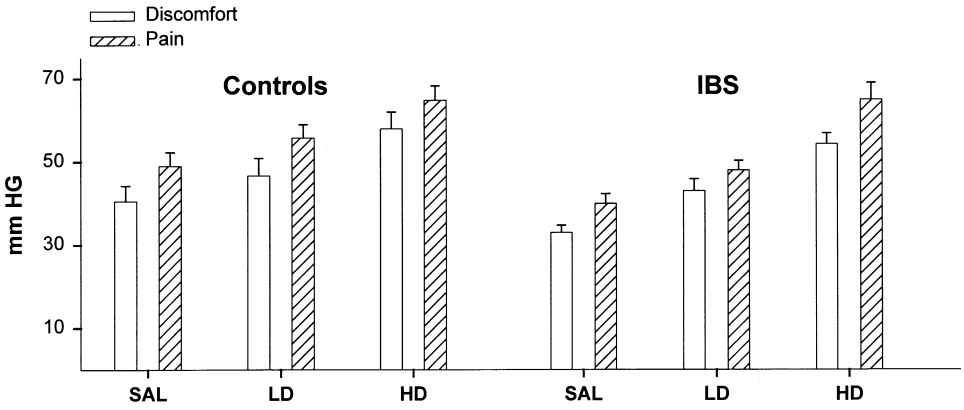

Fig. 1. Effect of fentanyl on perceptual thresholds for discomfort and pain during rectal distension for healthy control subjects ($n = 10$) and IBS patients ($n = 10$). Thresholds were obtained during phasic rectal distension using the threshold tracking paradigm as described in Section 2. Perception thresholds for discomfort (open bars) and pain (hatched bars) are shown during infusion of saline (SAL), low dose fentanyl (LD) and high dose fentanyl (HD). Shown are mean values ± SEM from subjects in each group.

3.3. Stimulus ratings obtained during fixed pressure stimuli

There was no evidence for a dose effect (LD versus HD) for intensity or unpleasantness ratings ($P > 0.25$); therefore, graphs and analyses were confined to SAL versus HD.

3.3.1. Normals

HD FEN significantly decreased the mean S-R curves for intensity and unpleasantness ratings in comparison to SAL ($P < 0.0001$). No significant interaction was present between rectal distension pressure and FEN. Intensity ratings during SAL infusion were significantly greater than during HD FEN for rectal distension pressures greater than 20 mmHg; unpleasantness ratings were significantly greater during SAL infusion, compared to HD FEN, for rectal distension pressures greater than 40 mmHg.

3.3.2. IBS

HD FEN significantly decreased the mean S-R curves for intensity and unpleasantness ratings in comparison to SAL ($P < 0.0001$). No significant interaction was present between rectal distension pressure and FEN. Intensity ratings were significantly greater during SAL infusion (compared to HD FEN) throughout the entire range of pressure steps. Unpleasantness ratings during SAL infusion were significantly greater for rectal distension pressures greater than 20 mmHg.

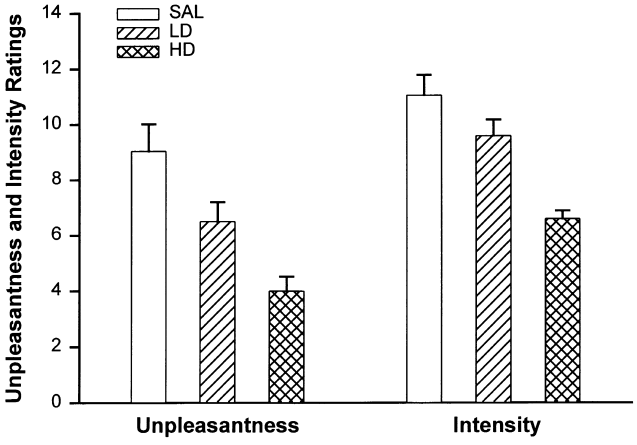

Fig. 2. Effect of fentanyl on intensity ratings during phasic rectal distension. Affective (left) and sensory (right) ratings of stimulus intensity obtained during the threshold tracking paradigm. Shown are mean values ± SEM from ten IBS patients.

3.3.3. IBS versus normals

Fig. 3 shows the S-R curves for IBS patients and normals for HD and SAL. No significant difference was seen for mean S-R curves for intensity ratings (Fig. 3a) between IBS patients and normals for SAL or HD FEN ($P > 0.50$). In contrast, mean S-R curves for unpleasantness ratings obtained during SAL infusion showed a statistically significant difference between IBS and normals ($P < 0.05$) (Fig. 3b). In the presence of FEN, the S-R relationship for IBS patients was flat, and not significantly different from the S-R curve obtained in normal control subjects.

3.3.4. Stimulus discrimination

There were no group differences or FEN effects on the omega^2 values computed from the fixed stimulus sensory ratings, indicating no differences in rating reliability or discrimination ability between the groups or across conditions.

3.4. Verbal descriptor ratings of rectal distensions

3.4.1. Normals

HD FEN had no significant effect on the percentage of subjects reporting individual verbal descriptors during fixed stimuli rectal distension at 40 mmHg (Fig. 4).

3.4.2. IBS

HD FEN significantly decreased the percentage of patients reporting abdominal discomfort, rectal fullness

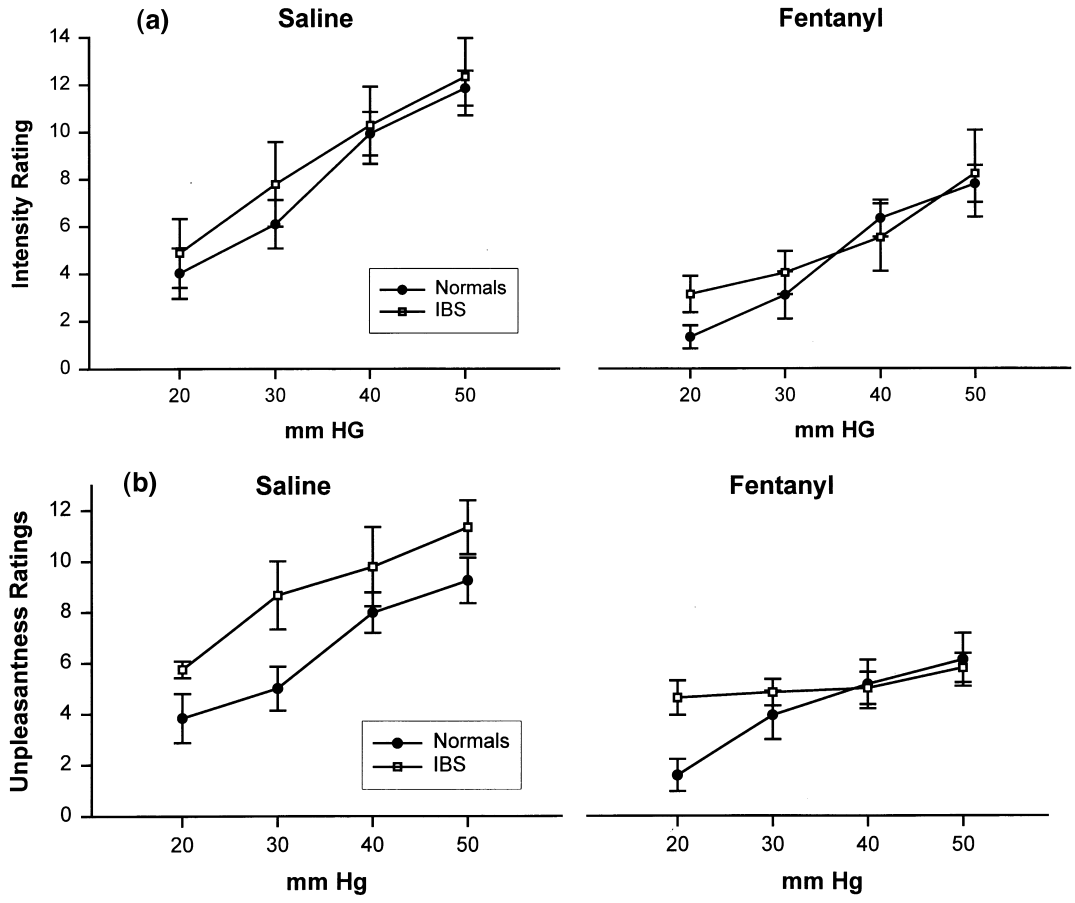

Fig. 3. Effect of fentanyl on stimulus-response curves for stimulus intensity ratings during phasic rectal distension. (a) Intensity ratings of stimulus intensity during normal saline (SAL) infusion and during high dose fentanyl (HD) infusion. (b) Unpleasantness ratings of stimulus intensity during SAL infusion and during HD infusion. Shown are mean values ± SEM from ten subjects in each group. Mean values for each subject for each stimulus were calculated from three trials. Closed circles are healthy control subjects, and open squares are IBS patients.

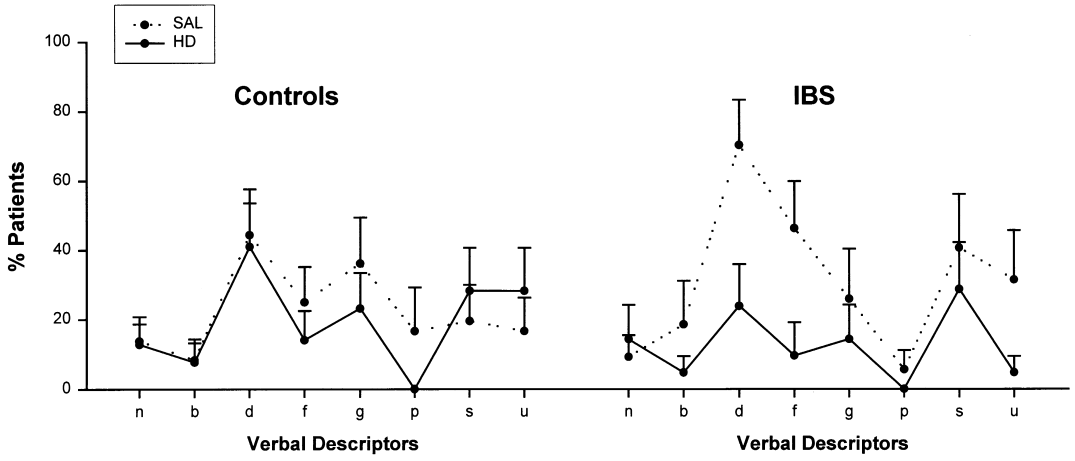

Fig. 4. Effect of fentanyl on verbal descriptor ratings of rectal distension. Shown are mean values ± SEM for the percentage of subjects in each group ($n = 10$ per group) reporting one of the following verbal descriptors during the fixed stimulus protocol: n, no sensation; b, bloating; d, discomfort; f, fullness; g, gas; p, pain; s, stool; u, urgency. Subjects were allowed to use more than one descriptor to characterize the experienced sensation. The hatched line indicates ratings during SAL infusion, and the solid line indicates ratings during HD infusion.

and urgency ($P < 0.05$) during fixed stimuli rectal distension at 40 mmHg (Fig. 4).

3.4.3. IBS versus normals

A significantly higher percentage of IBS patients reported the presence of rectal stool, urgency and abdominal discomfort during fixed stimuli rectal distension at 40 mmHg during SAL ($P < 0.05$), but not during HD FEN.

3.5. Cardiosympathetic and cardiovagal responses

The effect of FEN on cardiosympathetic (LF peakpower) and cardiovagal (HF peakpower) measures was evaluated during rectal sensory tracking.

3.5.1. Normals

FEN decreased LF peakpower (SAL 70 ± 9; LD 61 ± 9; HD 57 ± 6) ($P < 0.05$) but had no significant effect on HF peakpower (SAL 42 ± 9; LD 43 ± 9; HD 42 ± 8) in normals (Fig. 5).

3.5.2. IBS

FEN had no effect on LF peakpower (SAL 72 ± 6; LD 70 ± 9; HD 73 ± 4) or HF peakpower (SAL 31 ± 3; LD 27 ± 8; HD 30 ± 4) ($P = 0.4$) in IBS patients (Fig. 5).

3.5.3. IBS versus normals

IBS patients had significantly lower HF peakpower than controls for SAL (31 ± 3 versus 42 ± 9), LD (27 ± 8 versus 43 ± 9) and HD (30 ± 4 versus 42 ± 8) ($P < 0.05$). IBS patients had significantly higher LF peakpower than controls for HD (73 ± 4 versus 57 ± 6) ($P < 0.05$) but not for SAL or LD.

3.6. Rectal tone and compliance

FEN had no effect on the mean resting rectal tone in IBS patients (SAL 6 ± 3 ml; HD 8 ± 4 ml; $P = 0.43$) or normals (SAL 11 ± 7 ml; HD 9 ± 6 ml; $P = 0.60$). There was no significant difference in rectal tone between normals and IBS patients.

FEN had no effect on compliance in IBS patients (SAL 5.9 ± 0.7 ml/mmHg; HD 5.1 ± 0.9 ml/mmHg; $P = 0.52$) or normals (SAL 5.5 ± 0.6 ml/mmHg; HD 6.1 ± 0.7 ml/mmHg; $P = 0.63$). There was no significant difference in compliance between normals and IBS patients.

3.7. Mental status

3.7.1. Normals

Normals rated their overall performance as being slightly more impaired during HD FEN (2.7 ± 1.5) infusion than during normal saline infusion (SAL 1.66 ± 0.8), although this was not statistically significant ($P = 0.30$). Four of the seven (43%) subjects on FEN (LD or HD) correctly identified that they were receiving drug infusion on their initial visit while three of the four (75%) subjects on their initial visit correctly identified that they were receiving normal saline.

3.7.2. IBS

IBS patients also rated their overall performance as being slightly more impaired during FEN (HD 2.9 ± 2.0) infusion than during normal saline (SAL 0.8 ± 1.6) infusion; this was also not statistically significant ($P = 0.25$). Five of the seven (71%) patients on their initial visit correctly identified that they were receiving FEN (LD or HD) infusion while all four (100%) patients on their initial visit correctly identified that they were receiving normal saline infusion.

3.7.3. IBS versus normals

There was no difference in the mean overall performance or in the percentage of subjects who correctly identified whether or not they were receiving FEN.

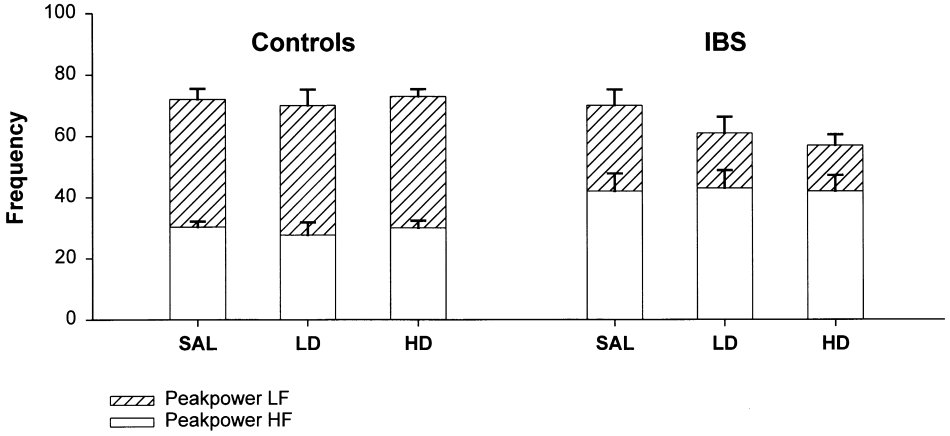

Fig. 5. Effect of fentanyl on cardioautonomic responses to rectal distension for healthy controls ($n = 10$) and IBS patients ($n = 10$). Shown are mean values ± SEM for peakpower for low frequency (LF) and high frequency (HF) components of heart rate variability obtained during the threshold tracking paradigm (10 min period of consecutive phasic rectal distension around the discomfort threshold). Hatched bars show the LF (cardiosympathetic) component, and solid bars show the HF (cardiovagal) component.

4. Discussion

We have shown for both healthy control subjects and IBS patients that a dose of i.v. FEN, which has minimal effect on mental status, can attenuate the perception of phasic rectal distension, as measured in terms of thresholds for discomfort and pain, ratings of intensity and unpleasantness of the stimulus, and verbal descriptor ratings. These effects were clearly seen in the non-painful range of stimulus intensities. The relative efficacy of FEN for these perceptual effects was greater in IBS patients. In addition, our findings demonstrate that the psychophysical methods used in this study were sensitive enough to detect the effect of a well established mu opioid analgesic compound (Maguire et al., 1992; McEnvoy, 1999) on perception of non-painful and painful visceral stimuli.

4.1. Effect of FEN on perception thresholds

As previously shown, IBS patients who also showed differences in S-R relationships had lower thresholds for discomfort and pain when assessed with a non-biased tracking paradigm (Naliboff et al., 1997). FEN dose dependently increased the perception thresholds in both healthy control subjects and in IBS patients. Thresholds for pain and discomfort were similar between the two groups during the high dose of FEN. Therefore, the relative potency of FEN on perception thresholds was greater in IBS patients than in normal subjects. Perception thresholds for discomfort as assessed by experimental rectal distension can probably not be considered nociceptive thresholds; they are not associated with significant heart rate responses and are significantly lower than visceral pain thresholds reported in the earlier literature (Lipkin and Sleisenger, 1957). Thus, the attenuating effect of FEN on perception thresholds was seen during non-nociceptive stimulus intensities.

To our knowledge, there are no other published studies on the effect of mu opioid agonists on perceptual responses to colorectal distension in humans. Fentanyl has been shown to have a dose-dependent effect on noxious cutaneous heat thresholds (Gracely and Naliboff, 1996). In a recent report, the effects of the kappa opioid receptor (KOR) agonist fedotozine on perceptual responses to distension of the left colon were reported (Delvaux et al., 1999). The authors concluded from their results that fedotozine reversed the colonic hypersensitivity of IBS patients via a specific effect on peripheral KORs on colonic afferents. However, this study only used a single trial of an ascending method of limits to assess perception thresholds (thereby maximizing response bias), and did not obtain S-R curves.

4.2. Effect of FEN on stimulus ratings

In addition to the assessment of perception thresholds, we measured stimulus ratings in terms of their perceived intensity and unpleasantness. Such stimulus ratings were assessed both during the threshold tracking paradigm and during a randomly delivered sequence of four stimulus intensities.

There was no difference in the intensity and unpleasantness ratings of the threshold tracking paradigm between control subjects and IBS patients. Thus, IBS patients used the same intensity and unpleasantness ratings to rate a stimulus that was 20% smaller than that experienced as discomfort by healthy subjects. These findings are consistent with the concept that both groups reliably used the scales to rate subjective sensations of intensity and unpleasantness (in this case the sensations at discomfort threshold) despite variation in the level of stimulus needed to produce that sensation (Gracely and Naliboff, 1996). FEN dose dependently decreased these ratings in both groups.

Stimulus-response curves established from the intensity ratings of randomly delivered stimuli of three fixed intensities were similar between healthy controls and IBS patients during saline infusion and during FEN infusion. FEN caused a rightward shift of similar magnitude in both study groups. In contrast, S-R curves for the unpleasantness ratings showed greater ratings in IBS patients during saline, but these differences did not remain in the presence of FEN. Thus, similar to the findings for thresholds of unpleasantness (discomfort), the relative potency of FEN to affect unpleasantness ratings of distensions was greater in IBS patients. Interestingly, in IBS patients, high dose FEN abolished the increase in unpleasantness ratings with increasing stimulus intensities. This observation, together with the fact that FEN normalized the higher unpleasantness ratings of all stimuli by IBS patients but had similar effects on the intensity ratings by both groups, is consistent with FEN having a greater effect on brain regions concerned with the attribution of unpleasantness to a visceral stimulus. The lack of group or condition differences in stimulus discrimination makes it unlikely that the FEN effects were due to changes in rating reliability.

4.3. Effect of FEN on cardioautonomic measures

During rectal sensory tracking, FEN significantly lowered cardiosympathetic tone in normal subjects while it had no effect on IBS patients. Thus, while cardiosympathetic tone was not different between the groups during saline infusion, it was significantly higher in IBS patients during HD FEN. The ineffectiveness of FEN to reduce sympathetic outflow to the heart may be related to the previously reported evidence for enhanced regulation of cardiosympathetic and other sympathetic outflow in subgroups of IBS patients (Esler and Goulston, 1973; Aggarwal et al., 1994; Heitkemper et al., 1994; Karling et al., 1998; Munakata et al., 1998).

The reason for the diminished response of cardiosympathetic outflow to FEN remains to be determined. Similar to the central effects of opioids on antinociception, networks of regions within the cortex, midbrain and brainstem are involved in mediating autonomic responses (Loewy, 1991). Many of the regions involved in central autonomic

control and antinociception overlap, such as the medial prefrontal cortex, the PAG, amygdala, hypothalamus and RVM. However, the central neurons and the opioid receptors which mediate antinociceptive and autonomic responses are likely to differ. For example, while mu and delta opioid receptor agonists injected into subregions of the PAG both produce analgesia, the two agonists have opposite effects on cardiovascular responses (Keay et al., 1997).

Possible confounding variables for the observed differences in the effect of FEN between patients and control subjects are an effect of the drug on mental status and on the mechanoelastic properties of the bowel wall.

4.4. Effect of FEN on mental status

There was no significant difference between subjective ratings of mental status impairment between patients and control subjects, and high dose FEN produced only a small increase in this impairment in the IBS group. Furthermore, FEN had no differential effect on the ability of the two study populations to discriminate between the different stimulus intensities.

4.5. Effect of FEN on rectal tone

Mu opioid receptors located in the brain, spinal cord and periphery (enteric nervous system) and spinal delta receptors contribute to the opioid effects on GI motility (Burks et al., 1988). The mechanism whereby opioids alter colonic transit appears to be due to both a reduction in the frequency of high amplitude propagating contractions in the colon (Kaufman et al., 1988) and a decrease in colonic tone (Steadman et al., 1992). Mu opioid receptor-induced changes in rectal tone could therefore affect the rectal pressure-volume relationship, thereby altering perception thresholds. However, no differences were observed in terms of the volume required to maintain the resting pressure of 5 mmHg between stimuli. Furthermore, differences in perception thresholds were observed regardless of whether stimulus intensity was expressed as pressure or as wall tension. There are several possible explanations for the apparent lack of an opioid effect on the mechanoelastic properties of the rectum: (1) in humans, opioids affect colonic transit most significantly in the proximal colon (Schang et al., 1986); (2) furthermore, it has been shown in healthy volunteers that the descending colon appears to relax 70–90 min after infusion of intravenous morphine (Schang et al., 1986), i.e. considerably later than the experimental period in the current study.

4.6. Possible mechanisms

Systemically applied MOR agonists exert their analgesic and antinociceptive effect by interacting with MORs on widely distributed neural networks involving peripheral, spinal and supraspinal sites. While some of the supraspinal sites (i.e. PAG) may play a primary role in antinociception, others may be more important in terms of attention, arousal and affective dimension of the experience. In general, opioids are thought to be fairly selective in their ability to attenuate noxious inputs and to have only modest effects on non-noxious somatic sensations. The fact that the most prominent effects were observed during stimulus intensities below the noxious range suggests that with the dose of FEN used in this study, and given the experimental design, the primary effects were related to such attentional mechanisms.

Within the human brain, MORs have been localized within most brain regions, with the exception of the somatosensory cortex (Simon and Hiller, 1978; Pfeiffer et al., 1982; Warmsley et al., 1982; Atweh and Kuhar, 1983). Using [^{11}C]diprenorphine and positron emission tomography, Jones et al. (1991a,b) and Vogt et al. (1995) demonstrated the highest density of MORs in brain regions commonly referred to as the medial pain system, including the perigenual cingulate and prefrontal cortices, the medial thalamus and the PAG. Recent studies using $H_2^{15}O$ PET have demonstrated the effect of FEN on distinct regional brain activity in the absence and presence of somatic heat pain (Adler et al., 1997). Of particular importance for the current study may be the finding that FEN (1.5 mg/kg i.v.) increased perigenual cingulate and inferior prefrontal cortical activation. We have shown in preliminary studies that IBS patients show less activation of perigenual cingulate in anticipation of visceral pain compared to healthy control subjects (Silverman et al., 1997). This subregion of the anterior cingulate cortex which has projections to the PAG has been suggested to play a role in a variety of functions including attentional and affective processes, autonomic responses and antinociceptive responses (Devinsky et al., 1995).

One may therefore speculate that FEN had a greater attenuating effect on the perception of the unpleasantness of visceral stimuli by activating brain regions, such as the perigenual anterior cingulate and prefrontal cortices and possibly PAG that have been found to show a blunted response to the anticipation of an unpleasant visceral stimulus in IBS patients.

In summary, we have shown that the MOR-preferring agonist FEN attenuates the perception of phasic rectal distension in a dose-dependent fashion. FEN also attenuates unpleasantness ratings during rectal fixed stimuli. The relative efficacy was greater in IBS patients than in normal subjects. These findings support our hypothesis that IBS patients may have a diminished release of endogenous opioids in response to visceral aversive stimulation.

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